TRIAL WATCH

Trends in COVID-19 therapeutic clinical trials

The COVID-19 pandemic has stimulated intense efforts to find effective therapeutics for all stages of the disease. Unfortunately, the scope, scientific rigour and clinical value of research activities undertaken worldwide have been difficult to gauge, especially amid the rapidly evolving landscape. From the very beginning of the search for effective preventive and therapeutic agents, the US Food and Drug Administration (FDA) has been committed to helping to identify and develop evidence-based therapeutics through well-designed clinical trials. It is critically important to protect patients from inefficacious or unsafe drugs while advancing those evidence-based efforts efficiently — without duplication or otherwise wasting resources — to bring effective interventions to patients. To inform such efforts, the FDA has sought a comprehensive understanding of the global COVID-19 clinical trials landscape. Here, we present our assessment of ongoing COVID-19 therapeutic clinical development efforts worldwide.

Surveying the clinical trial landscape

To develop a clear picture of the COVID-19 clinical trials ecosystem, FDA scientists within the Center for Drug Evaluation and Research (CDER) conducted an assessment of clinical development efforts worldwide, focusing on data from ongoing interventional clinical trials for potential COVID-19 drugs registered through ClinicalTrials.gov and the World Health Organization International Clinical Trial Registry Platform (WHO ICTRP). At the close of our broad assessment, we had identified more than 2,024 trials (separable into 2,895 individual treatment arms), encompassing total enrolment in excess of 500,000 patients. We estimate that our focus (that is, open interventional trials of drug products and antibody-based agents) represents about one-third of all COVID-19 trials (that is, with the overall total including observational studies and trials of vaccines and other non-drug agents) entered into the major international registries. The processes and reasoning followed in exploring the international clinical trial registries and the selection of trial data into a working database for our analyses are detailed in Supplementary Figs 1 & 2 and Supplementary Table 1.

We observed a steady increase in the number of trials through most of 2020, starting at 443 trial arms in March and rising ~29% each month until October. An additional 543 trial arms were initiated in April, defining the peak monthly rate of launched trial arms in 2020 (Supplementary Fig. 3). The distribution of therapeutic classes shifted over time (FIG. 1), perhaps indicating clinical experience over the course of the pandemic. In March, most trial arms were either antivirals (31%) or immunomodulators (31%), with the next most numerous class being combination trials (17%). By October, antivirals (17%) and immunomodulators (26%) had decreased in share, while neutralizing antibodies (9%) and other (29%) had increased. This shift was probably driven in part by the finding of lack of efficacy for hydroxychloroquine and some other repurposed drugs, coupled with the emergence of clinical testing of neutralizing antibodies. Efforts to exploit passive immunity to SARS-CoV-2 led to the clinical evaluation of convalescent plasma and related products (for example, neutralizing antibodies).

Assessing clinical impact

As regulatory actions, even during a pandemic, must be evidence-based, we assessed information about whether trials are randomized and sufficiently powered at the trial arm level. Whereas registered trials generally detail whether they are randomized, their statistical power, reflecting whether a sufficient number of patients will be enrolled in order to detect a given treatment effect, is not directly accessible from trial registry data.

Based on the planned enrolment number for a registered trial, however, and making a few simple assumptions (for example, distributing the planned enrolment number equally among trial arms), we estimated the percentage of trial arms from our total of 2,895 that could conceivably have reached a set of given enrolment thresholds (FIG. 2). We chose threshold values of enrolment in consideration of disease severity, based on FDA collective experience, such that an enrolment of 500 was chosen, for example, with regard to the cohort of patients hospitalized with lower respiratory infections. We then determined that 50 of the 1,396 trial arms for this patient cohort enrolled 500 or more such patients. FIGURE 2 shows that, although the stringency of the threshold criteria we selected could be varied considerably, our overarching conclusion remains that approximately 5% of the total COVID-19 trial arms in our assessment could be described as randomized and adequately powered. The 5% of global trial arms that are both randomized and adequately powered represent 26% of the total planned enrolment of 530,692 patients (FIG. 3).

Discussion and conclusions

A therapeutic trial ecosystem should possess two key capabilities in order to respond efficiently and effectively to an outbreak of a previously unknown disease such as COVID-19. First, a robust screening mechanism is needed, whereby repurposed drug candidates can be prioritized via mechanistic or nonclinical information and rapidly evaluated for the outbreak-related indications. The second requirement is a system to rapidly and efficiently generate definitive, highly actionable information on safety, efficacy and target population, of a quality that would be deemed acceptable by regulators and expert groups charged with establishing standard of care. Both these capabilities should be highly responsive to emerging information relevant to standard of care or from trial results. Furthermore, when the course of disease is

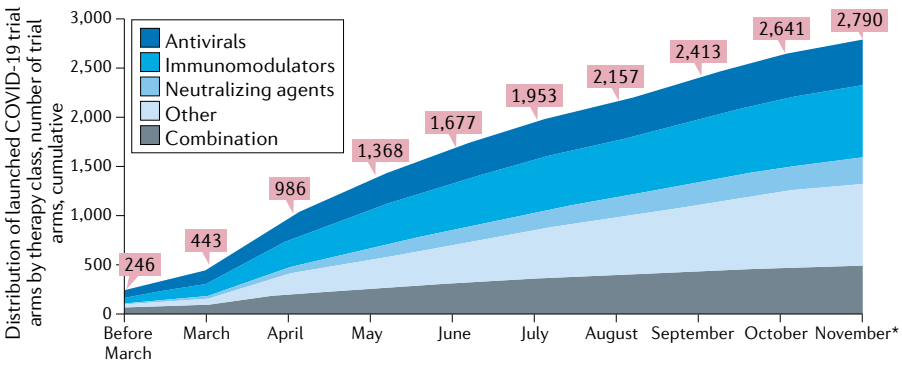

Fig. 1 | **Expansion of the clinical trial landscape for COVID-19 therapeutics in 2020.** Source: ClinicalTrials.gov and WHO clinical trial registry. *As of 20 Nov 2020. See Supplementary information for details.

Target patient cohort	Percentage change to randomized, adequately powered enrolment thresholds						
	−50%	**−25%**	**−10%**	**Baseline**	**+10%**	**+25%**	**+50%**
Post-exposure prophylaxis, pre-exposure prophylaxis or recovered (*n* = 302) Number of randomized, adequately powered arms (*enrolment threshold*)	2 (*2,500*)	1 (*3,750*)	1 (*4,500*)	1 (*5,000*)	1 (*5,500*)	1 (*6,250*)	1 (*7,500*)
Asymptomatic or mild disease (*n* = 367) Number of randomized, adequately powered arms (*enrolment threshold*)	33 (*500*)	23 (*750*)	21 (*900*)	18 (*1,000*)	13 (*1,100*)	11 (*1,250*)	10 (*1,500*)
Hospitalized with lower respiratory infection (*n* = 1,396) Number of randomized, adequately powered arms (*enrolment threshold*)	125 (*25*)	77 (*375*)	56 (*450*)	50 (*500*)	46 (*550*)	38 (*625*)	32 (*750*)
Ventilated in intensive care unit (*n* = 428) Number of randomized, adequately powered arms (*enrolment threshold*)	100 (*125*)	82 (*188*)	73 (*225*)	73 (*250*)	3 (*275*)	28 (*313*)	24 (*375*)
Total (*n* = 2,895) Number of randomized, adequately powered arms (**percentage**)	260 (**9%**)	183 (**6%**)	151 (**5%**)	142 (**5%**)	123 (**4%**)	78 (**3%**)	67 (**2%**)
	Less stringent thresholds				More stringent thresholds		

Fig. 2 | **Trials of COVID-19 drug candidates that may be considered adequately powered by consideration of enrolment thresholds.** There were also 402 trial arms for which the target patient cohort was unclear, which are not shown. Source: ClinicalTrials.gov and WHO clinical trials registry; accessed 20 Nov 2020. See Supplementary information for details.

as complex as it is in the case of COVID-19, multiple stages and presentations of disease must be adequately evaluated with respect to candidate drugs that enter clinical trials.

The analysis of our database has revealed gaps in these capabilities. The most important finding in our assessment is that the vast majority of trials of therapeutics for COVID-19 are not designed to yield actionable information; low randomization rates and underpowered outcome data render matters of safety and efficacy generally uninterpretable. Many of these trials are classified as phase II (FIG. 3), indicating procedural barriers to the generation of pivotal data. Especially within the urgent context of the pandemic, rapid screening and seamless phase II–III transitions should facilitate efficient go/no-go decision-making that will preserve resources and optimize enrolment. Notably, we observed great duplication of effort among registered trial arms, with multiple small trials studying similar interventions in similar populations.

The data analysis in this assessment also allows us to evaluate the ecosystem's reaction to critical findings, such as lack of evidence of efficacy for hydroxychloroquine. Additionally, we can assess the type and speed of response from different sponsors (academic compared with industry; Supplementary Fig. 4), growth in early-stage or late-stage trials, and representation of different geographies. Our data allow us to probe gaps in the clinical development landscape; for example, the insufficiency of investigation we see into pre-exposure and post-exposure prophylaxis (FIG. 2). Finally, we can ask fundamental questions about trial performance during a pandemic. How does trial design affect trial status and results when under the pressures of a rapidly changing public health emergency, and what factors are correlated with any notable trends?

As the COVID-19 pandemic continues, we will continue to assess pertinent factors of the trials landscape as a way of informing national and global COVID-19 response efforts. At the same time, we must continue to identify opportunities for readying our clinical development environment for greater patient impact in the context of public health emergencies.

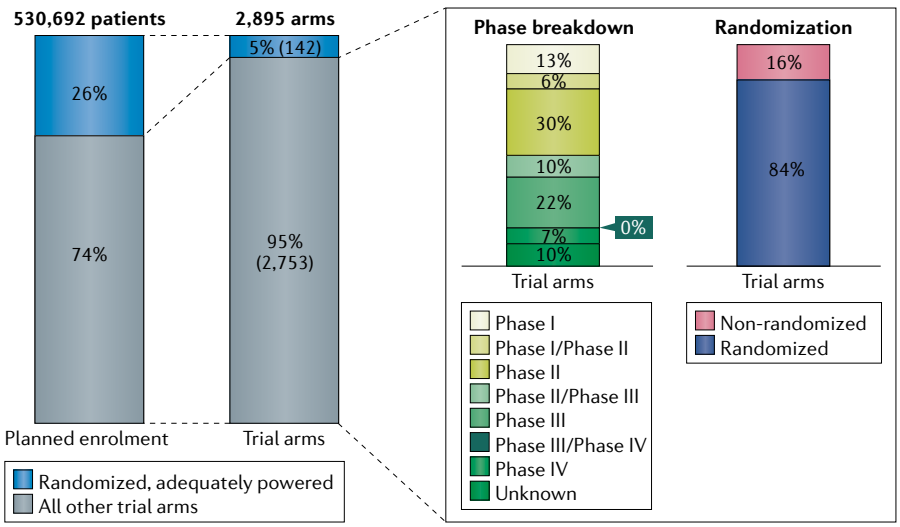

Fig. 3 | **Resource utilization in the clinical trial landscape for COVID-19 therapeutics.** Of 2,895 trial arms, ~5% could be considered randomized and adequately powered, and only about a quarter of enrolled patients contributed to adequately powered and well-controlled trials. The characteristics of the ~95% of other trials arms are shown to the right. Source: ClinicalTrials.gov and WHO clinical trial registry; accessed 20 Nov 2020. See Supplementary information for details.

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Competing interests
The authors are US government employees and declare no competing interests.

Supplementary information
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